There are two basic forms of Alzheimer’s disease (AD). The common (>95%) form is sporadic, and is caused by the failure to clear the Aβ peptide (mean age at onset 80 years). The rare (<5%) autosomal dominant familial form is caused by the over-production of Aβ42 (mean age at onset 45 years). In both forms, the kinetics of Aβ accumulation are similar, taking about 30 years to accumulate a total of approximately 7mg of Aβ. Thus we estimate that sporadic AD starts about the age of 50 years and the autosomal dominant form starts about 15 years of age. The advent of validated biomarkers (PET/CSF Aβ and tau) now provides us with unprecedented opportunities for preclinical diagnosis, enabling the development of primary and secondary prevention strategies. Predictive algorithms utilizing age, biomarkers, polygenic and vascular risk scores are now being developed from longitudinal cohort studies to estimate times of onset and rates of cognitive decline.

Most Aβ in the brain (>93%) exists in the urea/detergent/formic acid extractable fractions. A disease-modifying strategy needs to keep the total brain Aβ burden close to normal levels (<2 mg) to prevent or delay onset. Such a strategy may encompass lowering production, stabilizing or neutralizing the toxic Aβ species, and promoting Aβ clearance from the brain. We calculate that a 20% improvement in clearance of Aβ may be sufficient to delay onset by five years, if a therapy commences at the Aβ-PET cut-off of 1.4 SUVR, 20 years before onset. Proportionally, a 40% treatment effect would be required if started 10 years before onset, and an 80% effect would be required five years before onset. These objectives should be achievable using combinations of passive immunotherapies, stabilizers of non-toxic Aβ species, and BACE inhibitors.

The ultimate goal is primary prevention using therapeutic strategies or interventions which keep Aβ levels below the 1.4 SUVR threshold. Clinical trials aimed at this objective are now being planned.